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REVISED 10/15/85

Microfiche No.		
OTS0514386-3		
New Doc I.D.	Old Doc I.D.	
85-900000248	8EHQ-0590-0741	
Date Produced	Date Received	TSCA section
	5/15/90	8E
Submitting Organization		
CHEM MFGB ASSN		
Contractor		
Document Title		
COMMENTS ON THE FINAL REPORT OF A TWO-YEAR STUDY CONDUCTED AT CIVO INSTITUTES ON POLYMERIC METHYLENE DIPHENYL DIISOCYANATE WITH COVER LETTER DATED 051190		
Chemical Category		
POLYMERIC METHYLENE DIPHENYL DIISOCYANATE		



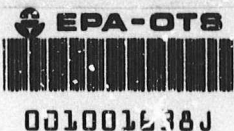
CHEMICAL MANUFACTURERS ASSOCIATION

CONTAINS NO CBI

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Vice President-Technical Director

4- Pages  
8EHQ-0590-0741 SUPP  
88-880000049 : PDCN

May 11, 1990



89-900000248

OTS DOCUMENT RECEIPT OFF.  
90 MAY 15 AM 11:48

Document Processing Center (TS-790)  
Office of Toxic Substances  
Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

Re: TSCA Section 8(e) Notice on Polymeric Diphenyl  
Methylene Diisocyanate Submitted by  
International Isocyanate Institute, Inc.  
(EPA Document Control No. 8EHQ-0786-0741)

Dear Sir/Madam:

We are pleased to submit the attached comments on behalf of the Chemical Manufacturers Association Diisocyanates Panel. The comments are in response to TSCA Section 8(e) submissions by the International Isocyanate Institute, Inc. (III). The initial Section 8(e) notice was submitted to EPA by III on July 5, 1988.

The III recently forwarded to the Agency the final report of its two-year study of polymeric methylene diphenyl diisocyanate (MDI) conducted at CIVO Institutes. The Diisocyanates Panel Toxicology Research Task Group (TRTG) reviewed the final report, and the enclosed comments summarize the review.



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If the Agency has questions or would like to discuss the comments further, please call Dr. Robert R. Romano, Manager, Diisocyanates Panel at (202) 887-1198.

Sincerely yours,

*Geraldine V. Cox*

Geraldine V. Cox, Ph.D.  
Vice President-Technical Director

Enclosure

COMMENTS ON THE FINAL REPORT OF A TWO-YEAR STUDY OF  
POLYMERIC METHYLENE DIPHENYL DIISOCYANATE (MDI)  
CONDUCTED AT CIVO INSTITUTES

Prepared by the Toxicology Research Task Group  
of the Chemical Manufacturers Association  
Diisocyanates Panel

The International Isocyanates Institute, Inc. (III) has recently submitted to EPA a final report of a two-year study of polymeric methylene diphenyl diisocyanate (MDI) conducted at CIVO Institutes, Zeist, The Netherlands. (EPA Document Control No. 8EHQ-0788-0741) The Chemical Manufacturers Association Diisocyanates Panel has asked its Toxicology Research Task Group (TRTG) to review the final report. In the following paragraphs, the TRTG provides a summary of the results of the study and comments on the significance of the reported results, followed by a detailed description of the study protocol.

Summary of Results

The full report of this study has recently been finalized after thorough quality assurance procedures and submitted to the Agency. Overall, the tumor incidence (both benign and malignant) and the number of animals with tumors were not affected by exposure to MDI. However, when considering each individual organ, there was a statistically significant incidence of a benign tumor of the lung (adenoma) in 6 of the 60 male rats exposed to 6 mg/M<sup>3</sup>, and an incidence of benign lung tumor (adenoma) in 2 of 59 female rats exposed to 6 mg/M<sup>3</sup> which was not statistically significant. In addition, 1 of 60 male rats exposed to 6 mg/M<sup>3</sup> showed a malignant tumor in its lungs (adenocarcinoma). No tumors were seen in the lungs of the rats exposed to either 1 mg/M or 0.2 mg/M<sup>3</sup>.

Significance of the Findings

The significance of the reported results is currently the subject of review by toxicologists and pathologists of the member companies of the International Isocyanate Institute. Preliminary evaluation suggests that the increased incidence of tumors in the lungs is consistent with the prolonged irritation and accumulation of material seen throughout the study. In the absence of prolonged high exposure leading to chronic irritation and lung damage it is highly unlikely that tumor formation could occur.



### Details of the Study

The study was carried out at an independent laboratory, CIVO-TNO, Zeist, The Netherlands, because of their international reputation in the field of inhalation toxicology. Despite determined efforts it was not possible to generate sufficient concentrations of MDI vapor, at ambient temperature, to produce toxicity to rats, the chosen species. Exposure of rats to MDI vapor would not therefore provide a Maximum Tolerated Dose (MTD) which would be necessary to provide a meaningful assessment of the chronic toxicology of MDI.

An MTD was achieved by generation of an aerosol, and since the formation of aerosol may occur in some applications of MDI, it was considered that the toxicology of MDI should be studied using MDI in the form of an aerosol.

The aerosol atmosphere consisted of particles of which 95% were less than 5 micron in diameter to ensure maximum penetration into the lungs. Polymeric MDI was chosen as the test substance since this is the most widely used MDI-based product. Exposure levels for a chronic study were selected following a series of 2 week and 13 week studies using rats. In these preliminary studies, the toxicity of MDI was confined to the respiratory tract where it caused irritation at levels of 4 mg/M<sup>3</sup> and above. The target concentrations for the chronic study were 0.0, 0.2, 1.0 and 6.0 mg/M<sup>3</sup>.

The study was carried out to internationally accepted guidelines for the determination of chronic toxicity and potential carcinogenicity. Male and female rats (cpb:Wu, Wistar Random), 60/sex/level, were exposed for 6 hours per day, 5 days per week for a period of at least 2 years to an atmosphere of respirable polymeric MDI aerosol. An interim sacrifice on a satellite group was performed on an additional 10 rats/sex/level at week 52. Animals on study were evaluated using clinical chemistry, hematological, urine analysis, gross and histopathological examination procedures.

The study progressed according to plan and the target atmospheric concentrations were achieved throughout. There were no effects seen outside the respiratory tract at any stage in the study. In animals killed after one year of exposure, those exposed to 6 mg/M<sup>3</sup> showed signs of irritation in the nose and lungs and some accumulation of yellow material in the lungs. At 1 mg/M<sup>3</sup> there were some indications of minor irritation, and 0.2 mg/M<sup>3</sup> was a clear no effect level.

Examination of the rats killed after two years of exposure showed that the irritation of the nose and lungs and the accumulation of the yellow material in the lungs continued in the rats exposed to 6 mg/M<sup>3</sup> of material. In the rats exposed to 1 mg/M<sup>3</sup> similar but lesser changes were observed, and again 0.2 mg/M<sup>3</sup> was a clear no effect level.

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